
يوم الأرض العربية

KIDNEY

ACS

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WHY……?


Two…friends
or foes

DEFINITION OF CRS

The CRS can generally be defined as a pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

five subtypes:

type I, acute CRS;

type II, chronic CRS;

type III, acute renocardiac syndrome;

type IV, chronic renocardiac syndrome;

type V, secondary CRS, meaning systemic diseases such as diabetes, sepsis and amyloidosis causing simultaneous cardiac and renal dysfunction .

the cardiorenal syndromes (CRS),

- **Pathophysiologic interconnections between the heart and kidneys‘**

’.

- acute kidney injury (AKI) is well recognized as an important complication in patients with ACS.
- incidence of 10 to 27% , and could be as high as 50% if ACS is complicated by cardiogenic shock .
- Development of AKI after AMI predicts short and long-term mortality , other major cardiovascular outcomes and long-term risk of end stage renal disease (ESRD).

- Patients hospitalized for ACS are subjective to several complications and interventional procedures associated with AKI, such as cardiogenic shock, heart failure, cardiac catheterization, and coronary artery bypass surgery .
- associated risk factors of AKI in these settings, including use of contrast agents, diabetes, previous kidney disease, hemodynamic instability, low cardiac output, and volume depletion

..

- Type 1 CRS, characterized by acute worsening of cardiac function leading to AKI, often complicates acute coronary syndrome (ACS) and acute decompensated heart failure (ADHF)
- Acute deterioration of cardiac function may set off a series of changes in **neurohormonal** and hemodynamic factors leading to arterial underfilling and venous congestion.
- Inadequate renal perfusion, increased intra-abdominal pressure and passive kidney congestion may culminate in AKI .
- .

- cardiac dysfunction and hemodynamic perturbations could result in systemic underfilling and renal hypoperfusion, leading to further renal injury
- . Neurohormonal activation, hypothalamic-pituitary stress reaction, and inflammation have also been shown to contribute to type 1 CRS
- . However, there is increasing evidence that it may be venous congestion rather than arterial underfilling that is associated decreasing renal blood flow and worsening renal function

- . Diastolic LV dysfunction, the earliest change seen after coronary occlusion results in elevated LV filling pressure and central venous pressure and transmitted back to the renal veins and result in direct renal dysfunction with impaired renal function and mortality in patients with cardiovascular diseases

Pathophysiology

- **Neurohormonal Factors:**
  - SNS, RAAS, AVP System
- **Hemodynamics:**
  - Loss of Cardiac Output
  - Transrenal perfusion pressure
  - Intrarenal hemodynamics

(Mechanisms in CRS)

(RASBIRE)

- RAAS
- Increased SNA
- Reactive oxygen species
- Inflammation
- Endothelin effect
- Argininevasopressin effects
- BNP effects

- In patients with cardiac diseases or undergoing cardiovascular surgery, new markers of renal dysfunction, such **as neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C**, have emerged as early markers of AKI prior to any elevations of serum creatinine and provide additional prognostic value.
- Levels of traditional cardiac markers, such as **natriuretic peptides and troponins** , rise in both cardiac and renal dysfunction, suggesting a bidirectional and reciprocal nature of the vicious circle of CRS

- ST2 (suppression of tumorigenicity 2), consisting of a trans-membrane ligand (ST2L) and a soluble form (sST2), is a member of the interleukin-1 receptor family &is a novel HF markers in response to mechanical stress .
- A serum levels sST2 rise in various cardiac diseases and have been shown to independently predict mortality and other adverse outcomes in HF and MI .

As a marker of mechanical stretch similar to the natriuretic peptides, sST2 has been demonstrated to significantly correlated with hemodynamics, LVEF, disease severity and adverse remodeling in AMI and , right ventricular hypokinesis and jugular venous distension in ADHF .

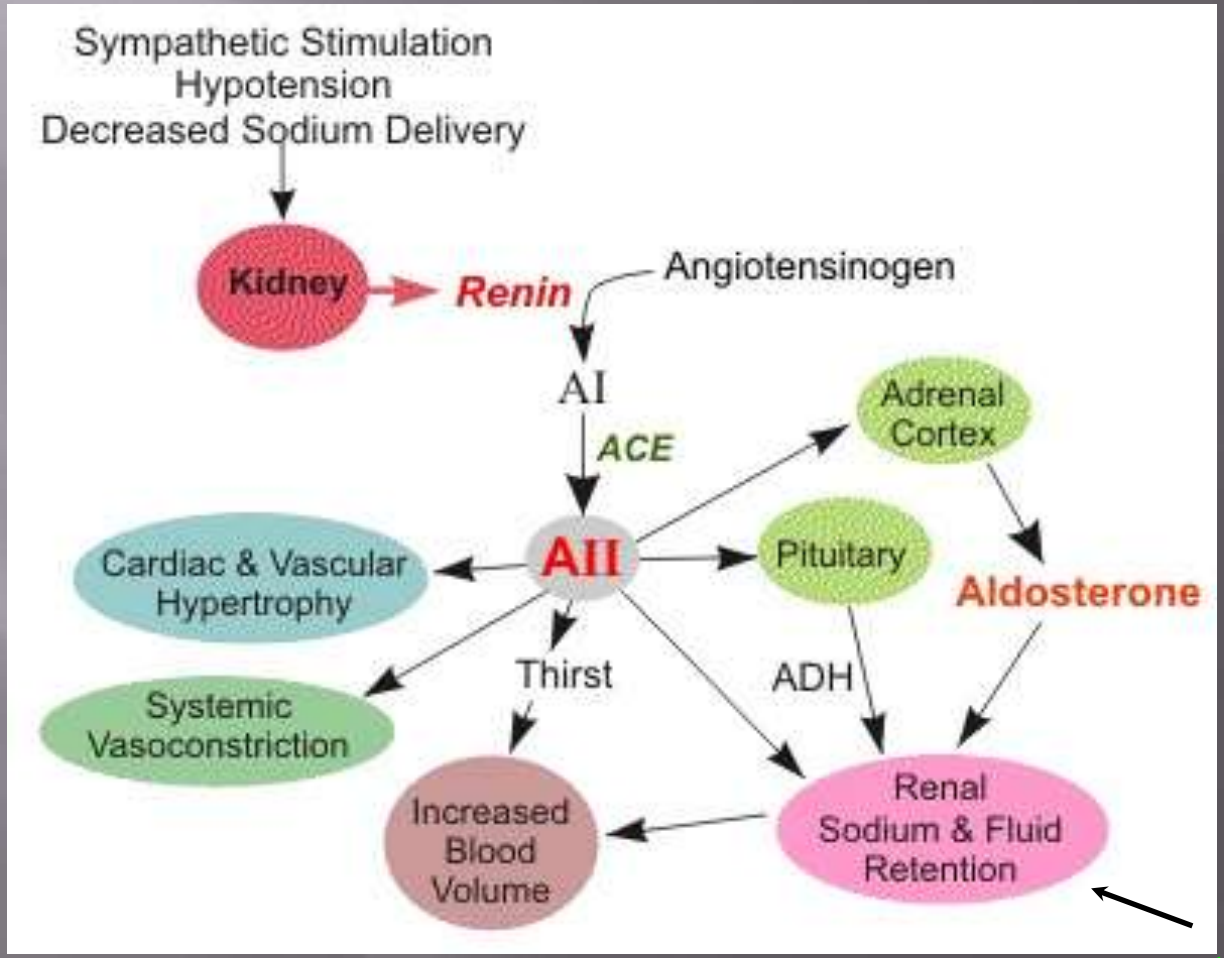
The association between sST2 and diabetes, hypertension and inflammatory markers not only suggests the role of ST2 as a cardiometabolic marker but implicates its potential in predicting AKI and CRS in acute cardiac events.

- Increased BNP levels indicated elevation of central venous pressure and passive renal congestion and could also serve as an indirect marker of AKI in AMI.
- combined biomarkers of HF and renal injury may provide incremental diagnostic values and improve risk stratification in STEMI patients developing AKI.

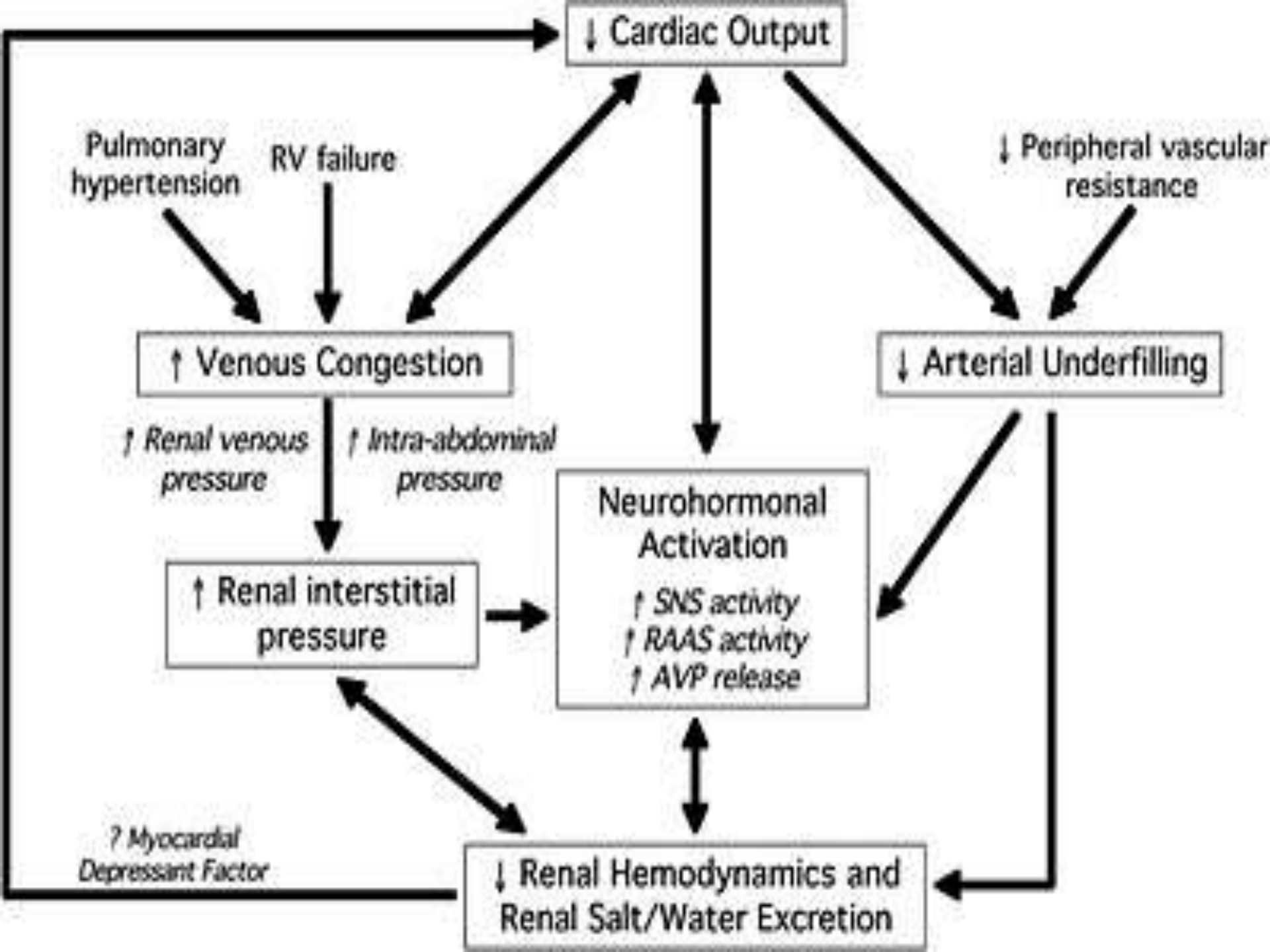
S

- combine the biomarkers of HF (BNP and sST2) and renal injury (NGAL and cystatin C) in the prediction of AKI in ACS patients undergoing (PCI).

Neurohormonal Axis



Adenosine


↓ Cardiac Output
Pulmonary hypertension
RV failure
↓ Peripheral vascular resistance
↑ Venous Congestion
↓ Arterial Underfilling
↑ Renal venous pressure
↑ Intra-abdominal pressure
Neurohormonal Activation
↑ SNS activity
↑ RAAS activity
↑ AVP release
↑ Renal interstitial pressure
? Myocardial Depressant Factor
↓ Renal Hemodynamics and Renal Salt/Water Excretion

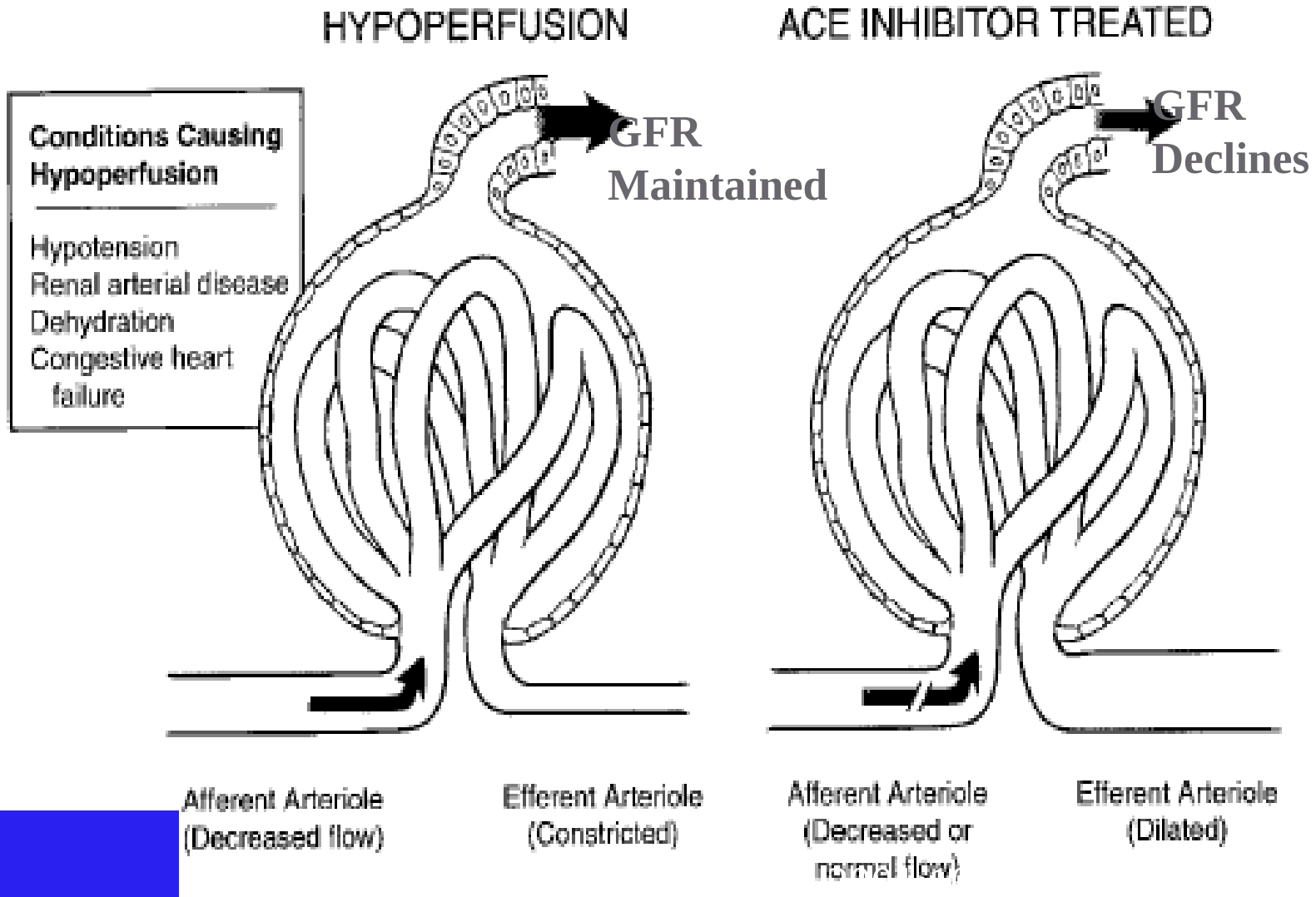
CHF patients at increased risk for CRS:

- Hypertension
- Diabetes
- Severe Vascular Disease
- Elderly

ACEI play a complex role in renal function in HF

- May improve CO in some patient and hence increase effective renal perfusion
- ACEI may lower BP to the point where effective renal perfusion is impaired
- With chronic renal disease, there is hyperfiltration in the remaining nephrons. ACEI decreases efferent arteriole constriction and hence decreases glomerular capillary pressure which may preserve renal function longterm
- This may result in a 10-20% increase in creatinine, but over the long term renal function is preserved

ACEI intolerance in low CO, low SVR states



Invasive hemodynamic monitoring should be considered in a patient:

- **who is refractory to initial therapy,**
- **whose volume status and cardiac filling pressures are unclear,**
- **who has clinically significant hypotension (typically SBP !80 mm Hg) or worsening renal function during therapy,**

Or

- **in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary .**

HFSA Guildelines 2010

Important molecules

- NGAL—neutophilgelatinase assosciated lipocalin.
- Cystatin C
- Kidney injury molecule 1
- glucosaminidase N acetyl β (D)
- Netrin 1
- NHE –sodium hydrogen exchanger
- GST –glutathione s transferase
- L FABP –l type fatty acid binding protein.
- IL-6,8,18

Anemia –a crucial factor in the vicious cycle of CRS

- **Integral part of advanced renal failure.**
- **Independent effect on CVD in CKD**
- **Every 1 gm/dl drop in mean hemoglobin –risk of cardiac failure increases by 25%.**
- **Increases LVH by 42%,increases death risk by 14%.**
- **.**

Role of ADMA

- Asymmetric dimethyl arginine
- *New emerging CV risk factor in uremic patients.*
- Competitive NO synthase inhibitor.
- Decreased NO availability.
- Degraded by dimethyl arginine dimethyl hydrolase – renal tissue.
- ADMA accumulates with renal failure.
- Second strongest predictor of CV mortality after Age.
- Reduced by ACEI ,ARBs,insulin sensitizers.

Angiotensin II

- RAAS –diabetics and HTN
- Angiotensin II –vasoactive peptide,true cytokine that regulates cell growth,inflammation and fibrosis.
- Increases TNF alpha,IL-6,NF kB
- Stimulates superoxide lipid peroxidation and inactivation of NO producing oxidative stress.
- Promotes atherosclerosis.
- Endothelial cell apoptosis
- .

Hyperhomocysteinemia

- Strong predictor of CVD in general population.
- Moderate levels 16-30umol/l in CKD.(4.4-10.8umol/L)
- Enhances vascular smooth muscle proliferation.
- Prothrombotic environment in coagulation.
- Activates factor V,X,XII.
- Decreased activation of protein C, thrombomodulin.
- Modualtion of annexin II.
- Oxidative stress --- ROS—binding to NO--- homocysteinated acylated proteins—acc of S.-adenosyl homocysteine –inhibitor of transmethylation reactions.

??Adenosine

Elevated levels seen in ADHF ▣

Released locally in response to stress (Macula Densa) and sodium delivery to the DCT ▣

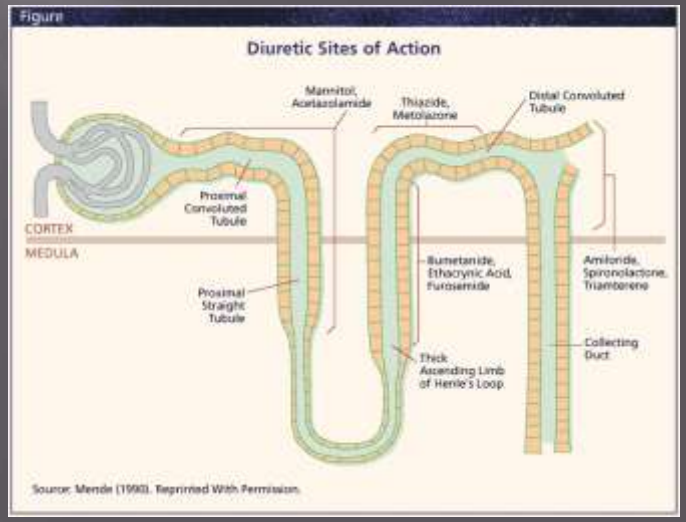
:Actions ▣

Afferent Arteriole Vasoconstriction ▫

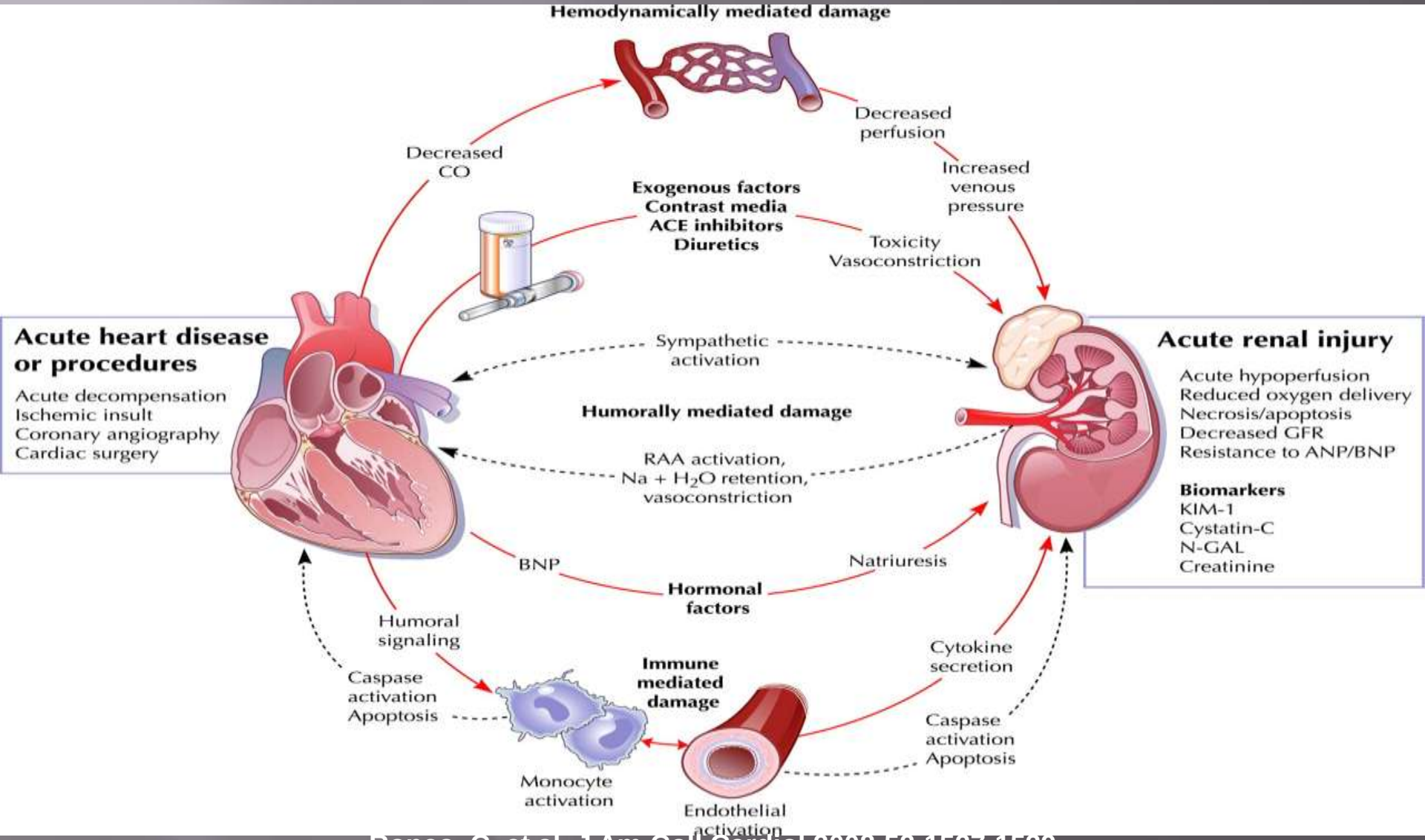
Decreased GFR ▪

Sodium reabsorption ▫

Tubuloglomerular feedback mechanism for regulation of GFR ▫



CRS Type 1



Ronco, C. et al. J Am Coll Cardiol 2008;52:1527-1539

- Early diagnosis of CRS type 1 is important as serum creatinine rises when the AKI is already established.
- Novel biomarkers are needed –rise within few hours of onset of AKI
- NGAL –neutrophil gelatinase assosiated lipocalin – earliest and sensitive marker of ischemic/nephrotoxic injury detected in blood /urine.
- Kidney injury molecule 1 is a highly specific marker for ischemic AKI.

Biomarkers in the diagnosis of AKI

Biomarker	Assosciated injury
Cystatin C	Proximal tubule injury
KIM 1	Ischemia and nephrotoxins
NGAL	Ischemia and nephrotoxins
NHE3	Ischemia,prerenal ,postrenal AKI
α GST	Proximal tubule injury ,acute rejection
π GST	Distal tubule injury,acute rejection
L-FABP	Ischemia and nephrotoxins
Cyr 6 1	Ischemic ATN
NETRIN 1	Ischemia and nephrotoxins,sepsis

CI-AKI

CI-AKI

- a rise of serum creatinine of 0.5 mg/dL or a 25% relative rise in creatinine at 48 hours after contrast exposure.
- 2% to 25% of patients undergoing PCI.
- Because accumulation of creatinine is relatively slow, it requires 48 to 72 hours to identify many cases of CI-AKI.
- Evaluation of creatinine at 24 hours after contrast exposure only will allow identification of patients who will develop CI-AKI .

- rapidly increasing markers of GFR such as cystatin C allow more accurate estimation of CI-AKI incidence at the 24-hour time point.

- Smaller changes in serum creatinine as an absolute increase of 0.3 mg/dLpermit earlier identification of kidney injury and poor outcome in patients undergoing coronary angiography.

risk stratification for the development of CI-AKI on the basis of

(1)Comorbidities

estimated glomerular filtration rate <60 mL · min^{-1} · 1.72 m^{-2},

diabetes mellitus,

congestive heart failure) .

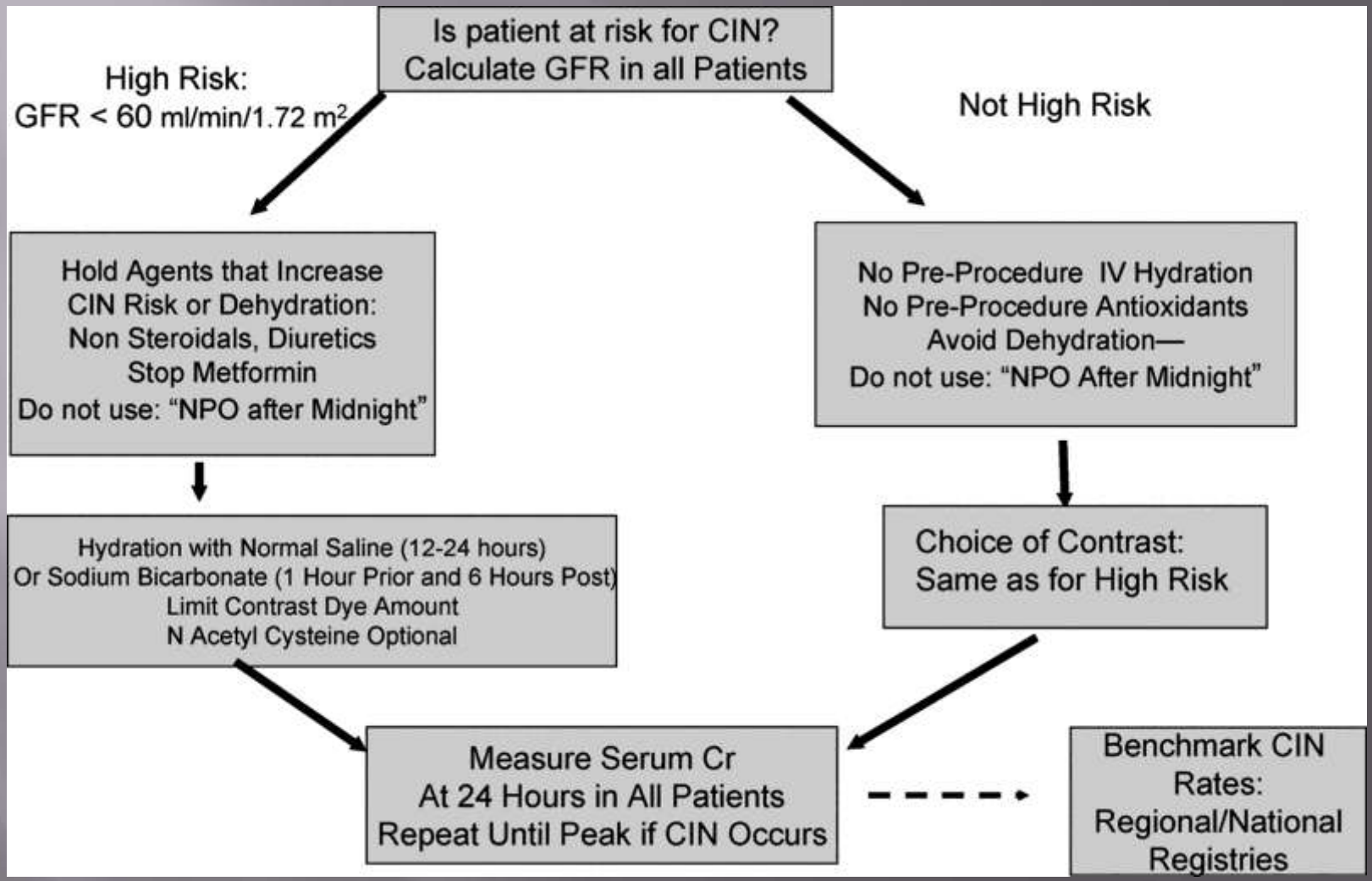
(2) procedural variables

contrast volume,

requirement for intra-aortic balloon pump).

can predict a post–PCI range of CI-AKI from a rate of 7% lowest risk to >50% highest risk score.

A sample algorithm for risk stratification, potential prevention, and assessment of CI-AKI occurrence.



Richard Solomon, and Harold L. Dauerman Circulation. 2010;122:2451-2455

Management of CRS 1

Diuretics –useful in volume overloaded non hypotensive patients.

Loop diuretics ,thiazides

Overzealous use –worsening renal function

Exacerbates neuro hormonal activity , activates RAAS , Inc SVR ,worsens LVF .

Inotropes --dopamine,dobutamine,milirinone

Vasodialtors – nesiritide

Ultrafiltration(aquapheresis)

Arginine vasopressin receptor antagonists—tolvaptan

EVEREST trial

Adenosine A1 receptor antagonists

Treatment of the Cardiorenal Syndrome

5 important questions…

- What is the fluid status? ⊡
- Is the blood pressure adequate for renal perfusion? ⊡
- What is the cardiac output? ⊡
- Is there evidence of high central venous pressure? ⊡
- Is there intrinsic renal disease? ⊡

Profiles of the Cardiorenal Syndrome

	CRS due to:	Fluid Status	CO CI	SVR	Proteinuria	Treatment
	**Too Dry!!!**	Dry	Low	Nml or high	None	Fluids, stop diuretics
	**Too Wet!!! (high CVP)**	Wet	Nml	Nml	None	Continuous diuretic infusion, distal tubular diuretic, ultrafiltration
	**Too Clamped Down!!!**	Wet or Nml	Low	High	None	ACEI, Nitroprusside, Nesiritide, Relaxin
	**Vasodilated!!!**	Nml or wet	Nml or high	Low	None	Stop ACEI, Pressors, Vasopressin Inotropes, VAD
	**No Pump!!!**	Wet or Nml	Low	Nml	None	Inotropes, Vasopressors Balloon Pump LVAD
	**Intrinsic Renal Disease/Diuretic Resistance**	Wet	Nml	Nml	None	Continuous diuretic infusion, distal tubular diuretic, ultrafiltration

Hypovolemic Cardiorenal

Too Dry!!!

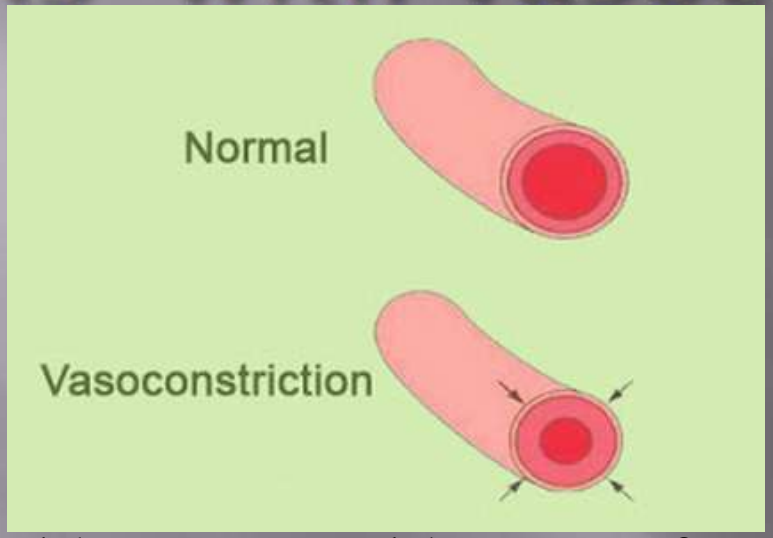
- **Overdiuresed or intercurrent illness results involume loss and renal dysfunction**
- **Give fluids, stop diuretics and IV vasodilators**
- **Often a reluctance to give fluids to HF patients but it may be critical in this situation and time is of the essence to avoid irreversible renal damage**

CRS due to high central venous pressure

Too Wet!!!

- **Poor renal perfusion due to high central venous pressure**
- **Usually CVP > 15-20 mm Hg coupled with reduced blood pressure**
- **Diuretics often held because of worsening renal function and misguided idea of " intravascular volume depletion"**
- **Continue diuretics to reduce central venous pressure**
- Ultrafiltration

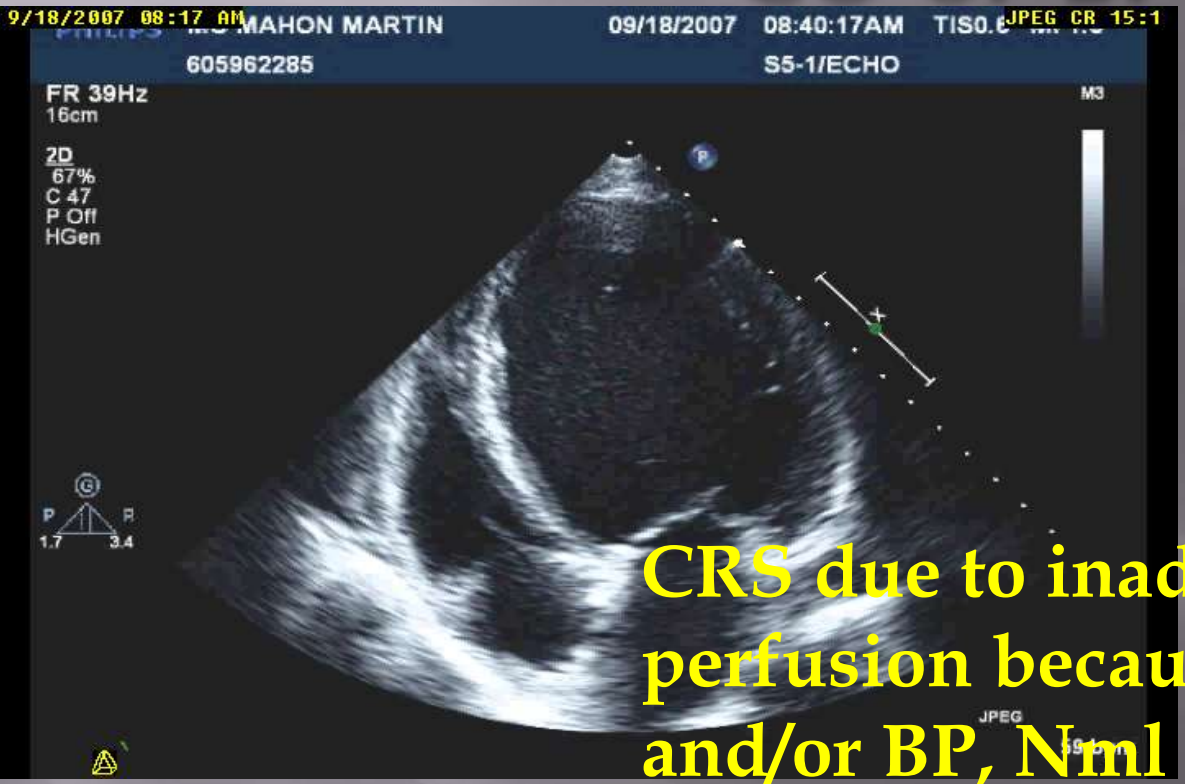
CRS with vasoconstriction



Clamped Down!!!

- Low CO and hence renal hypoperfusion due to HF mediated vasoconstriction (Ang II, endothelin induced increased afterload)
- CO is low and SVR high, often over 1800-2000
- ACEI and vasodilators very useful since CO can increase significantly if afterload normalized. Actual improvement in renal function may be seen
- May need temporary inotropic support if systolic BP <80 as vasodilators are added

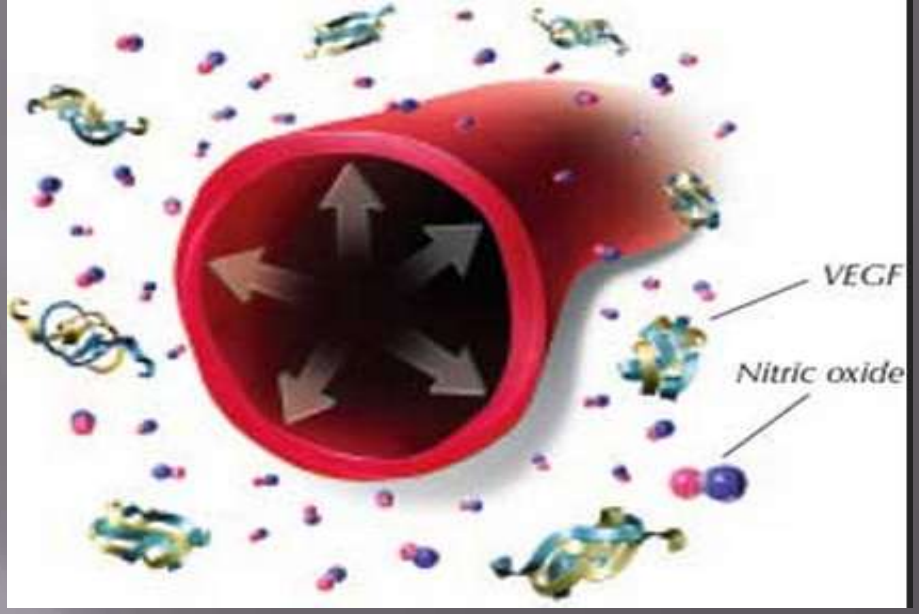
CRS with normal SVR but low CO or BP " No Pump!!!"



- **CRS due to inadequate renal perfusion because of low CO and/or BP, Nml SVR!!!**
- **Inotropes, Pressors, Temporary circulatory support**
- **LVAD**

CRS with vasodilation

"Vasodilated!!"



- Renal hypoperfusion due to low perfusion; CO may be normal but SVR and BP low
- Vasodilators worsen BP and hence renal perfusion
- Stop of ACEI, especially if SVR is low
- Rule out sepsis
- Pressors, Inotropes, ? Vasopressin
- Consider transplant or ventricular assist device if renal dysfunction is felt to be reversible

CRS with normal CO and SVR

"It's the Kidneys, Not the Heart!!!!"
"

- **Consider intrinsic renal disease (IRD) or diuretic resistance syndrome, renal artery stenosis**
- **Probable IRD when long hx of HTN and/or diabetes, look for proteinuria, renal artery stenosis**
- **Trial of loop diuretic infusion, combination with distal tubular diuretic**
- **Add nesiritide**
- **Consider ultrafiltration**


Lastly

Increase in Creatinine without AKI

Inhibition of tubular creatinine secretion

Trimethoprim, Cimetidine, Probenecid

Interference with creatinine assays in the lab (false elevation)

acetoacetate, ascorbic acid, cefoxitin

flucytosine

Increase in BUN without AKI

Increased production

GI Bleeding

Catabolic states (Prolonged ICU stay)

Corticosteroids

Protein loads (TPN-Albumin infusion)

Take home message

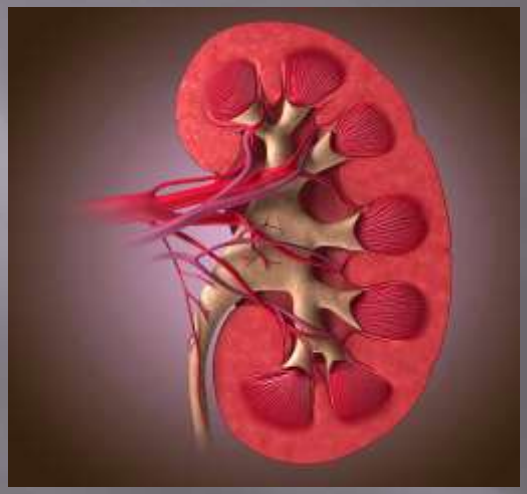
- CRS is a pathophysiological condition.
- Treatment is to be individualized based on the etiology.
- Early diagnosis is important for better survival.
- Early novel biomarkers are to be used in diagnosis.

Future

- Pathophysiology of the syndrome to be known in detail.
- New alternative therapies other than diuretics are expected with results from large trials. .
- Diagnostic criteria to be developed.

an ideal biomarker in AKI, such as organ specific, highly sensitive for indicating renal injury, unaffected by other biomarkers, helpful in differential diagnosis and monitoring disease course and response to treatment

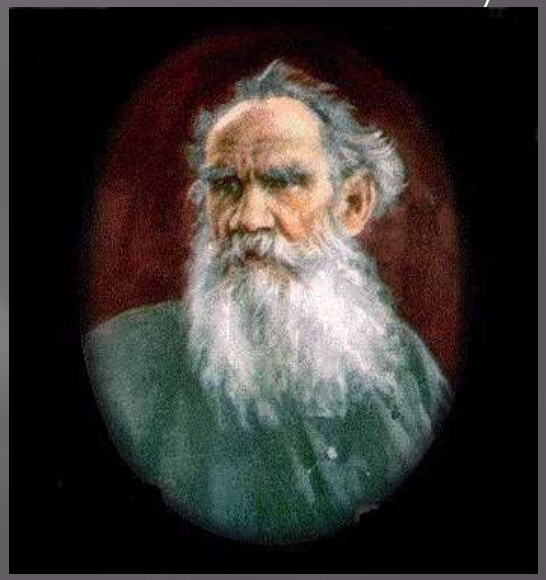
- . Because such an ideal biomarker is probably not available to date, a multi-marker model has been proposed for AKI for risk prediction, early diagnosis .



Thank You

Literary Last Note

"All happy families are all alike, all unhappy families are unhappy in their own way." *Anna Karenina* Leo Tolstoy



All patients compensated HF patients are alike,
all patients with cardiorenal syndrome are unhappy in their own way.

Questions ?